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Inflammatory Markers of Coronary Risk

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The past decade has been characterized by growing interest in the idea that atherosclerosis is an inflammatory disease[1] and by the finding that serum levels of markers of inflammation can be used to predict the risk of cardiovascular events.[2] In this issue of the *Journal* are two reports — one by Lindahl et al.[3] and one by Packard et al.[4] — that advance our knowledge of these areas. Both studies made use of clinical trials to address whether levels of serum-based inflammatory markers were predictive of cardiovascular events.

Lindahl et al.[3] addressed whether serum levels of cardiac troponin T, C-reactive protein, and fibrinogen at the time of presentation of an acute coronary syndrome were predictive of the long-term risk of death from cardiac causes. Blood levels of troponin T are a well-established marker of myocardial damage and the short-term risk of death. Lindahl et al. demonstrated that levels of troponin T were also predictors of the long-term risk of death from cardiac causes (at a mean of three years). The levels of both C-reactive protein and fibrinogen were also predictive of the long-term risk of death from cardiac causes, though only C-reactive protein levels remained an independent predictor on multivariate analysis. There was only a weak correlation between troponin T levels and C-reactive protein levels, and both were independently predictive, suggesting that they may reflect different processes associated with the long-term risk of cardiovascular events.

Packard et al.[4] evaluated whether the levels of certain markers were predictive of the risk of coronary events among men with hypercholesterolemia but not preexisting coronary disease. Levels of C-

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reactive protein and fibrinogen were both predictive of the risk of coronary events; however, the strength of this association was significantly reduced when other, traditional cardiovascular risk factors were considered in the analysis.

The most interesting finding in this study is related to lipoprotein-associated phospholipase A_2, an enzyme that is also known as platelet-activating factor acetylhydrolase.[5] Lipoprotein-associated phospholipase A_2 circulates in the blood in association with both low-density lipoprotein (LDL) and high-density lipoprotein, and its levels are correlated with the levels of LDL cholesterol.[5] Interestingly, Packard et al. found that increased serum levels of lipoprotein-associated phospholipase A_2 were associated with an increased risk of a coronary event. The results may have been confounded by the fact that lipoprotein-associated phospholipase A_2 levels were also significantly correlated with LDL cholesterol levels, although this variable remained an independent risk factor after the inclusion of LDL cholesterol levels in the analysis.

Lipoprotein-associated phospholipase A_2 hydrolyzes the proinflammatory phospholipid platelet-activating factor, as well as structurally related oxidized phospholipids,[5] and injection of this enzyme into mice reduced local inflammation.[6] As a result, lipoprotein-associated phospholipase A_2 has been thought to inhibit inflammation and, by extension, possibly atherogenesis.[7] However, Packard et al. found that lipoprotein-associated phospholipase A_2 levels were positively associated with the risk of coronary events.

This study therefore raises the important question of whether lipoprotein-associated phospholipase A_2 is simply a marker of risk, perhaps an inflammatory marker, or directly promotes atherogenesis. Lipoprotein-associated phospholipase A_2 appears to be a marker of systemic inflammation, since levels in animals are substantially increased by an injection of endotoxin, its transcription is regulated by mediators of inflammation, and plasma levels are moderately increased in a variety of inflammatory conditions.[5] Interestingly, Packard et al. found no correlation between levels of C-reactive protein and levels of lipoprotein-associated phospholipase A_2.

Lipoprotein-associated phospholipase A_2 may promote atherogenesis, perhaps by hydrolyzing oxidized phospholipids into fragments that are more atherogenic than their parent compounds or by generating lysolecithin, which has a variety of proinflammatory properties. Studies in gene-knockout mice and pharmacologic-inhibition experiments in animals are re- quired to address whether a reduction in lipoprotein-associated phospholipase A_2 activity will reduce atherosclerosis. This issue should be studied with respect to all markers of future cardiovascular events, and the answers have potential implications for the development of therapies for the prevention and treatment of atherosclerosis and its sequelae.

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There are several potential sources of inflammatory markers as well as the cytokines that promote their production (Figure 1). Some of the most widely measured and discussed inflammatory markers are derived from the liver, including C-reactive protein, fibrinogen, and serum amyloid A. Their production is stimulated by systemic cytokines, which are themselves derived from a variety of sources. It is important that the production of hepatic inflammatory proteins is modulated by both genetic and environmental factors; the best example of this dual influence is fibrinogen, since levels are affected by polymorphisms in the fibrinogen gene as well as by smoking.[8] Little is known about the way in which genetic influences affect the production of C-reactive protein or serum amyloid A.

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Figure 1. Sources of Inflammatory Markers and Cytokines.

Some of the most commonly measured inflammatory markers, such as C-reactive protein, fibrinogen, and serum amyloid A, originate in the liver, and their production is stimulated by systemic cytokines such as interleukin-1ß, interleukin-6, and tumor necrosis factor α. Cytokines are produced at several extrahepatic sites, such as the heart, vessel walls, macrophages, and adipose tissue. These sites can produce other types of inflammatory markers as well. The heart secretes troponin T and I and creatine kinase MB in response to injury. The atherosclerotic vessel wall produces soluble adhesion molecules, such as intercellular adhesion molecule 1 (ICAM-1), vascular-cell adhesion molecule 1 (VCAM-1), E-selectin, and P-selectin. Macrophages secrete phospholipases in response to inflammation.

A second source of inflammatory markers is macrophages and related cells. One example is secretory phospholipase A_2, whose levels are elevated in acute and chronic inflammatory states and may predict the risk of events in patients with coronary disease.[9] Lipoprotein-associated phospholipase A_2 is also produced by macrophages and could be included in this group of inflammatory markers. The lack of a correlation between levels of C-reactive protein and levels of lipoprotein-associated phospholipase A_2 in the study by Packard et al. probably reflects the fact that they are produced by different tissues in response to different patterns of cytokines. The levels of both C-reactive protein and lipoprotein-associated phospholipase A_2 were independent predictors of the risk of cardiovascular events in that study.

A third source of inflammatory markers is the arterial wall itself, particularly endothelial and vascular smooth-muscle cells. Examples of markers in this category include soluble intercellular adhesion molecule 1 (ICAM-1), vascular-cell adhesion molecule 1, E-selectin, and P-selectin. These cell-surface molecules are expressed and up-regulated by cytokines, and proteolysis results in soluble fragments — the portions of these molecules that are actually measured in blood. In one study,

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soluble ICAM-1 levels were independently predictive of the risk of cardiovascular events.[10] Although soluble ICAM-1 levels were strongly correlated with C-reactive protein levels, adjustment for C-reactive protein levels did not substantially decrease the relative risk associated with an elevated level of soluble ICAM-1. This finding suggests that levels of soluble adhesion molecules may provide predictive information that is additive to the information provided by levels of liver-derived inflammatory markers.

Specific cytokines, particularly interleukin-1ß, interleukin-6, and tumor necrosis factor α, are largely responsible for the increased expression of inflammatory markers by the liver. In fact, in one study, serum levels of interleukin-6 were predictive of the risk of myocardial infarction, and although the levels of interleukin-6 were correlated with the levels of C-reactive protein, the association between interleukin-6 levels and the risk of myocardial infarction remained significant even after adjustment for the C-reactive protein level.[11] One source of cytokines could be the atherosclerotic plaque itself. However, alternative hypotheses should be considered.

The myocardium can be a source of cytokines, since the levels of cytokines are elevated in patients with acute myocardial necrosis as well as in those with chronic congestive heart failure. Could mild, subclinical ventricular dysfunction result in increased levels of cytokines and thereby contribute to the moderate elevations of inflammatory markers seen in prospective studies? Increased levels of cytokines could also represent a systemic response to chronic infection, providing a potential link between infection and cardiovascular disease. Finally, adipose tissue is increasingly recognized as a source of cytokines such as interleukin-1ß, interleukin-6, and tumor necrosis factor α. Studies of inflammatory markers have consistently shown a strong correlation between the levels of these markers and the levels of body fat, markers of insulin resistance, and other indicators of a dysmetabolic state.[12,13] Could levels of inflammatory markers primarily reflect either the presence of a depot of adipose tissue that increases the risk of cardiovascular events through its metabolic effects or the presence of a dysmetabolic state associated with the risk of coronary events?

What are the clinical implications of the finding of increasing numbers of serum-based inflammatory markers whose levels are predictive of the risk of cardiovascular events? It is now generally recognized that although the use of traditional risk factors produces reasonably accurate estimates of risk in populations, this approach allows clinicians to predict only about 50 to 60 percent of the variation in the absolute risk of an event in individual patients.[14] Therefore, the addition of other factors that would increase the predictive ability would also improve the accuracy of decisions regarding the use of proven preventive therapies.

In a direct comparison of the usefulness of levels of various serum-based markers, Ridker et al. found that the effects of inflammatory markers and those of lipids were clearly additive with respect to the ability to predict the risk of cardiovascular events.[15] The measurement of certain highly validated inflammatory markers, such as C-reactive protein, in selected patients may increase the accuracy of assessments of cardiovascular risk. Whether the levels of additional markers, such as soluble

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adhesion molecules or lipoprotein-associated phospholipase A_2, should also be used clinically as predictors of the long-term risk of cardiovascular events awaits further study.

There is still much to be learned about the mechanisms that link inflammatory markers to the risk of cardiovascular events, as well as the effect of treatments that reduce the levels of these markers. Progress in this field enhances our ability to predict the risk of such events, allows clinicians to administer preventive therapies to those most likely to benefit, provides potential new targets for the treatment of atherosclerosis, and promises to contribute to a new era of preventive cardiovascular medicine.

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